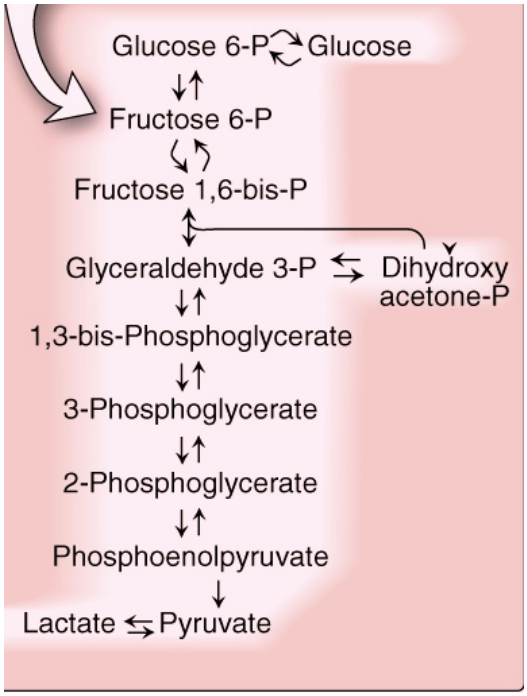
Glycolysis

Introduction to Metabolism
Regulation of Metabolism
Overview of Glycolysis
Reactions of Glycolysis

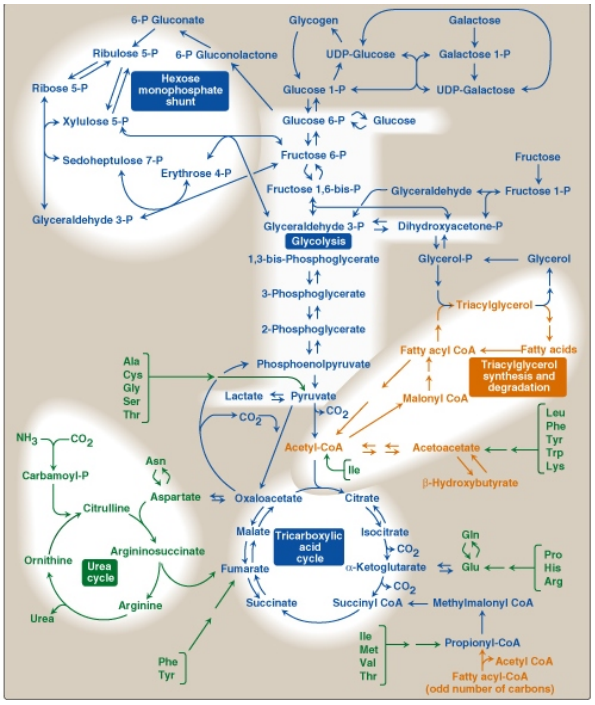
Suggested Reading:

Lippincot's Ilustrated reviews: Biochemistry

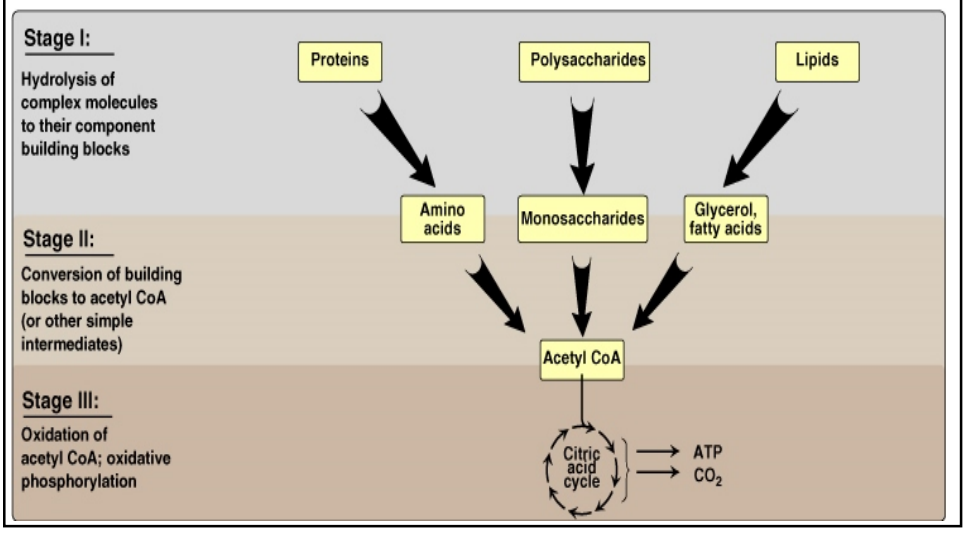


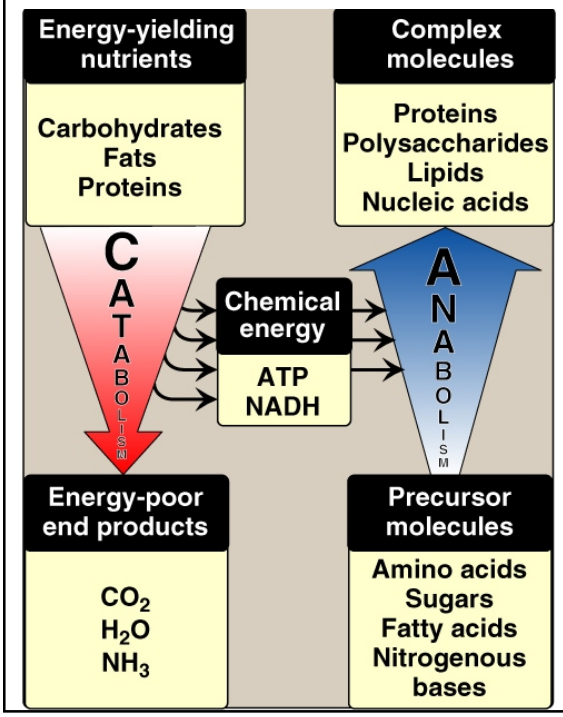
Glycolysis, an example of metabolic pathway

The product of one reaction is the substrate of the next reaction



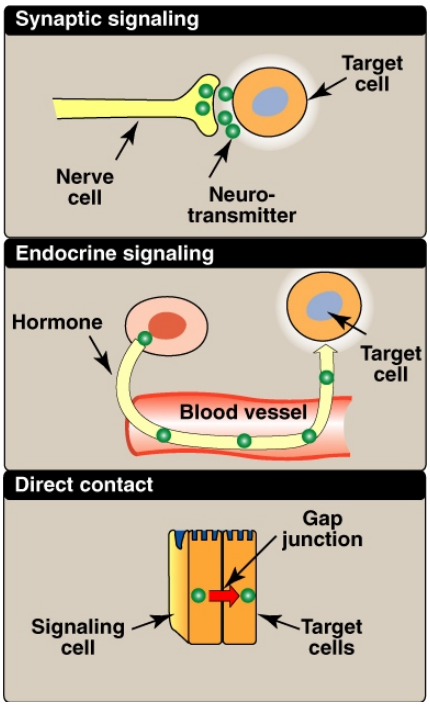
Metabolic pathways intersect to form network of chemical reactions



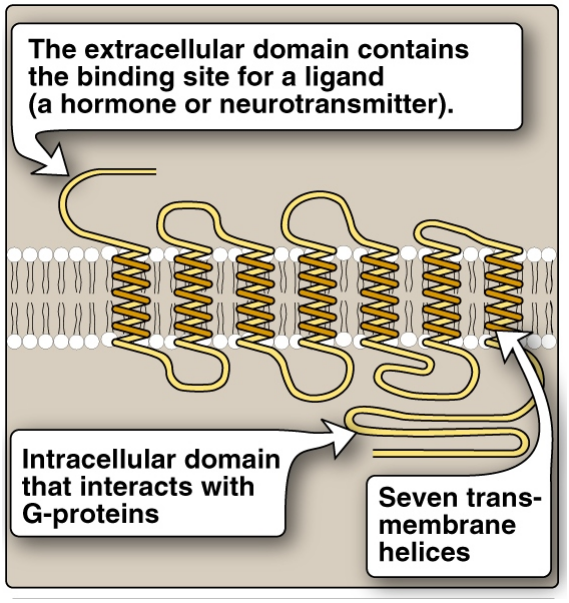


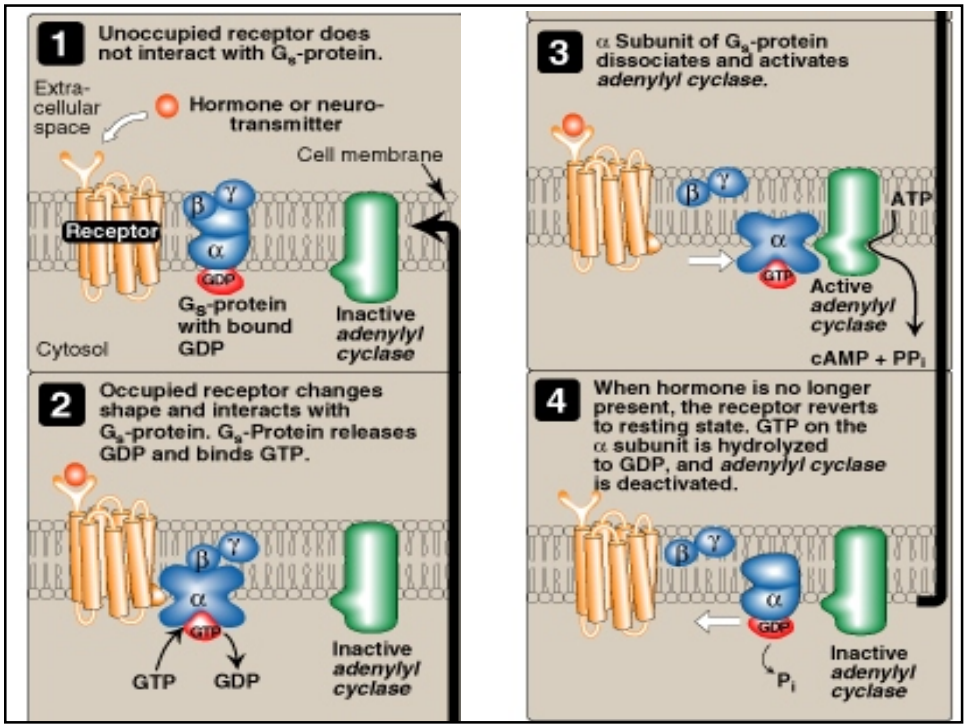
Regulation of Metabolism

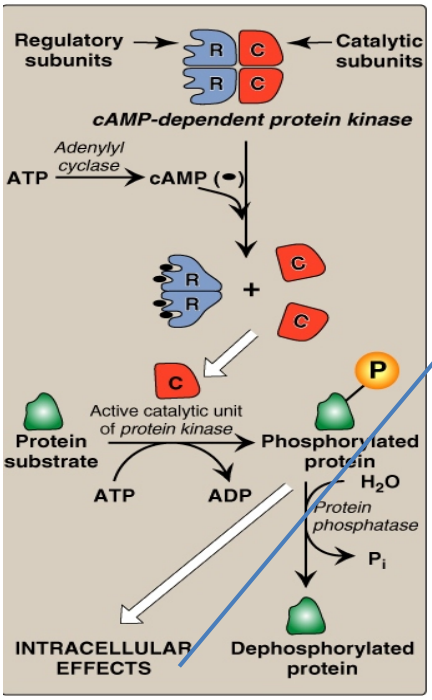
- Signals from within the cell
  - Substrate availability, product inhibition, allosteric
  - Rapid response, moment to moment
- Communication between cells (intercellular)
  - Slower response, longer range integration
- Second messenger
  - Ca^{2+} / phosphatidylinositol system
  - Adenylcyclase system



Communication between cells; Commonly used mechanisms







INTRACELLULAR EFEECTS
- Activated enzymes
- Inhibited Enzymes
- cell's ion channels
- bind to promoter

GLYCOLYSIS

Universal Pathway: In all cell types

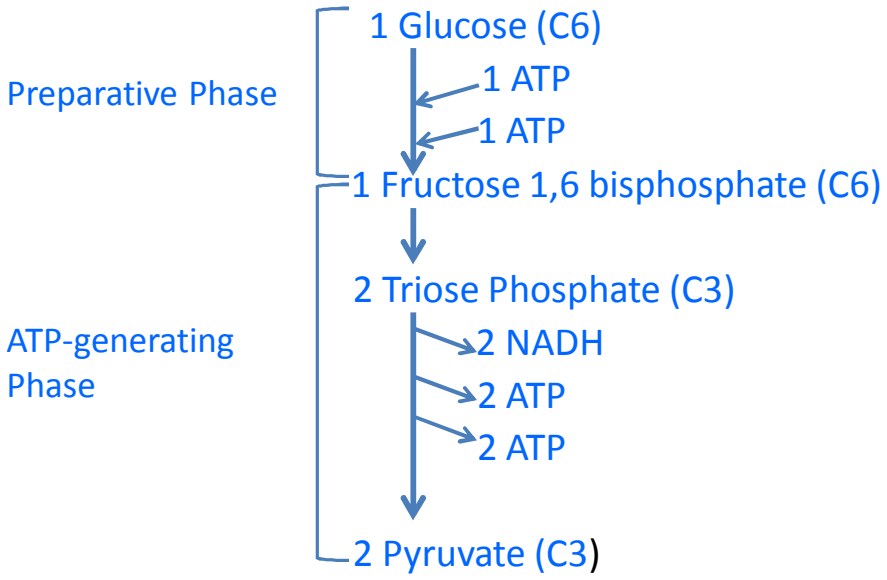
Generation of ATP

With or without O2

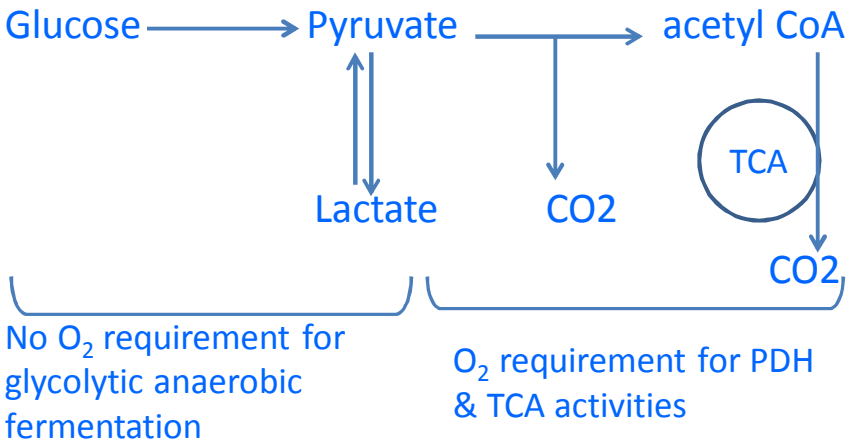
Anabolics Pathway:

→ biosynthetic precursors

The Two Phases of the glycolytic Pathway

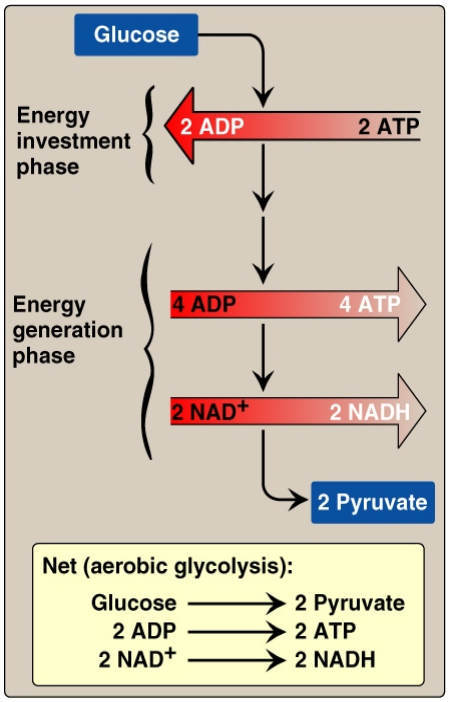


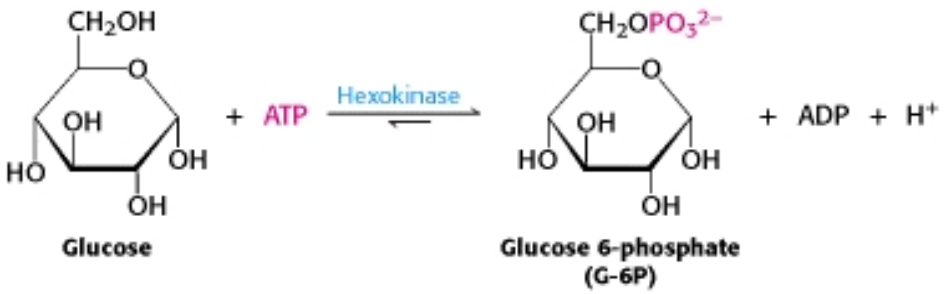
Glycolysis occurs in all human cells



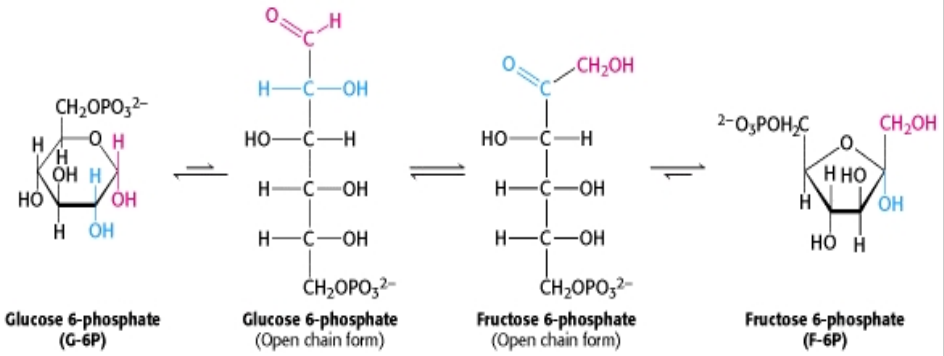
Tissues with an Absolute or high Requirement for Glucose

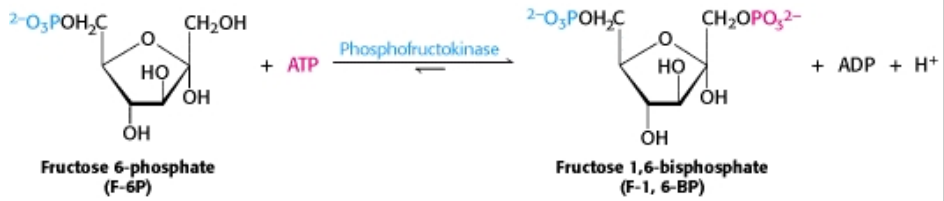
- Brain
- Red Blood Cells
- Cornea lens and retina
- Kidney Medulla,
- Testis
- Leukocytes
- White muscle fibers

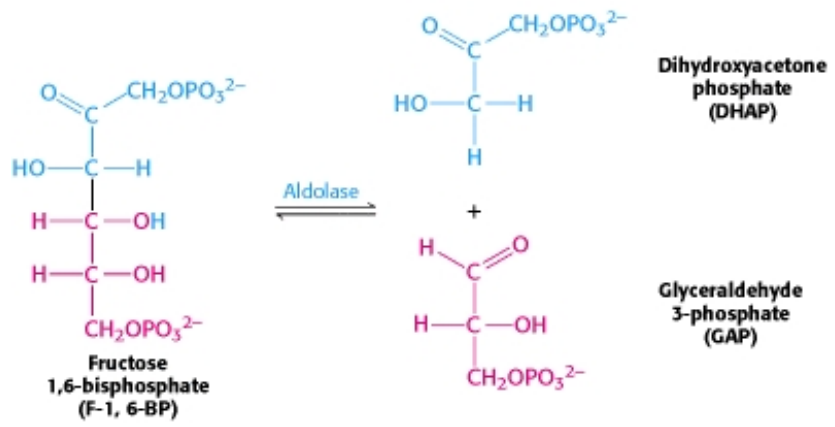


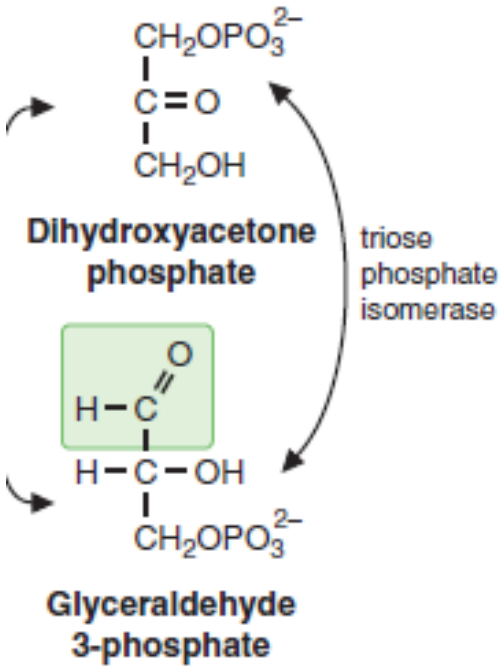


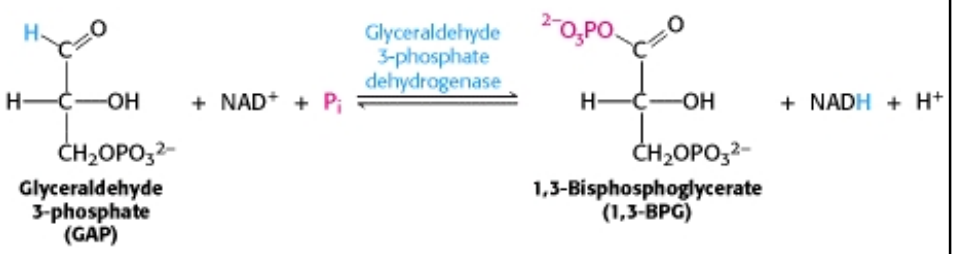
	Hexokinase	Glucokinase
Occurance	In all tissues	In liver
Km	< 0.02 mM	10-20 mM
Specificity	Glc., Fruc, Man, Gal	Glc.
induction	Not induced	↑ insulin, Glc
Function	At any glucose level	Only > 100 mg/dl

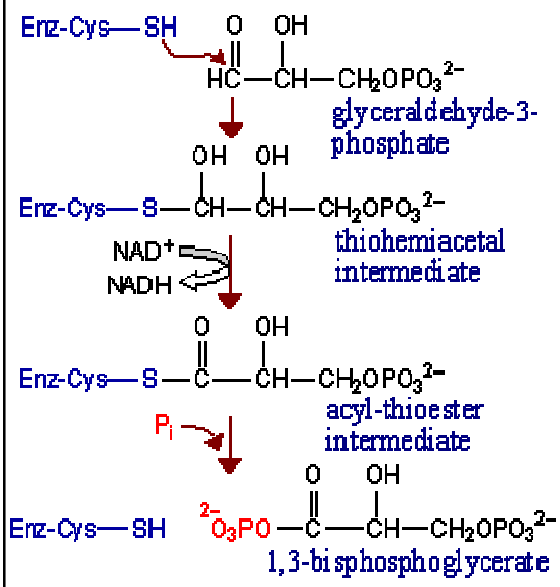

Glucose 6-phosphate
(G-6P)
Glucose 6-phosphate
(Open chain form)
Fructose 6-phosphate
(Open chain form)
Fructose 6-phosphate
(F-6P)


Phosphofructokinase
+ ATP
+ ADP + H+
Fructose 6-phosphate
(F-6P)
Fructose 1,6-bisphosphate
(F-1, 6-BP)


Fructose
1,6-bisphosphate
(F-1, 6-BP)
Aldolase
Dihydroxyacetone
phosphate
(DHAP)
Glyceraldehyde
3-phosphate
(GAP)


Dihydroxyacetone
phosphate
triose
phosphate
isomerase
Glyceraldehyde
3-phosphate





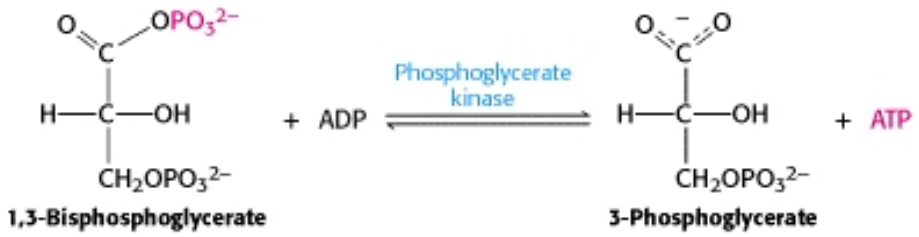
Mechanism of the reaction:

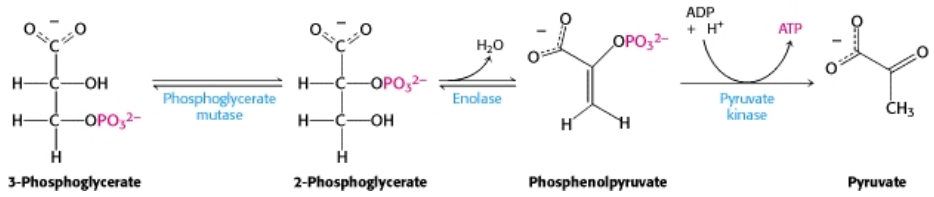
E and S form covalent linkage

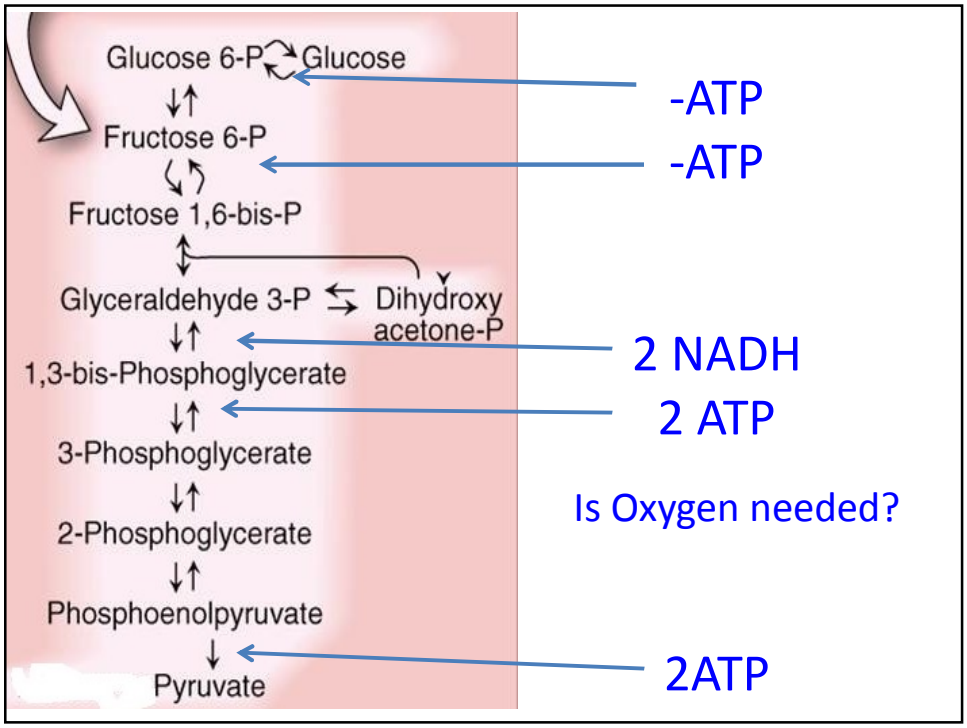
S is oxidized and NADH is formed

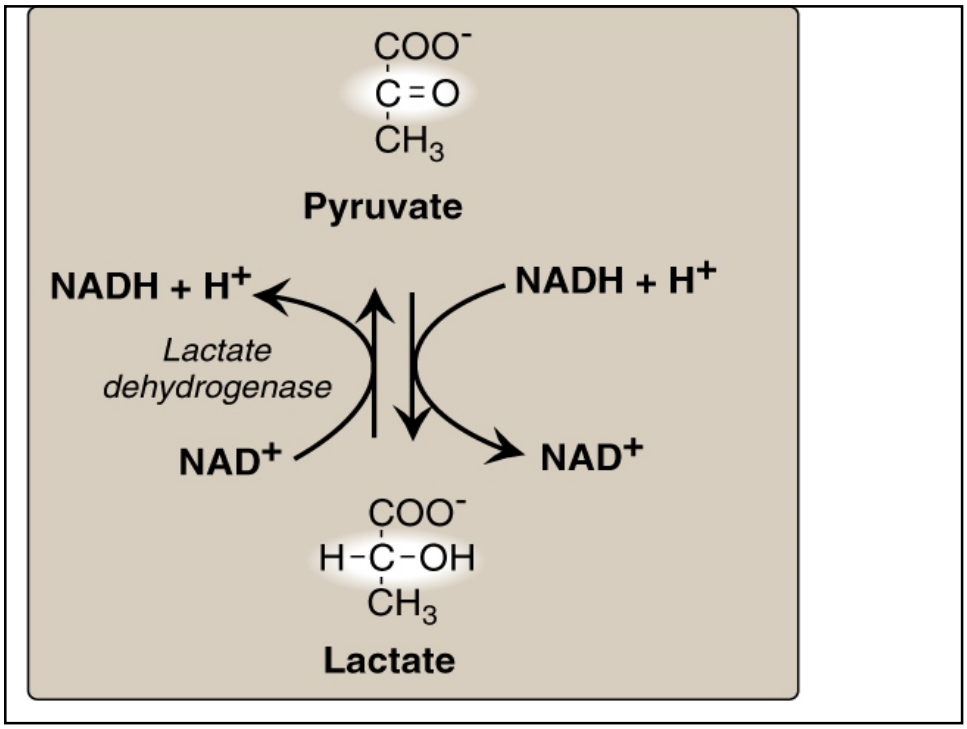
NADH is released

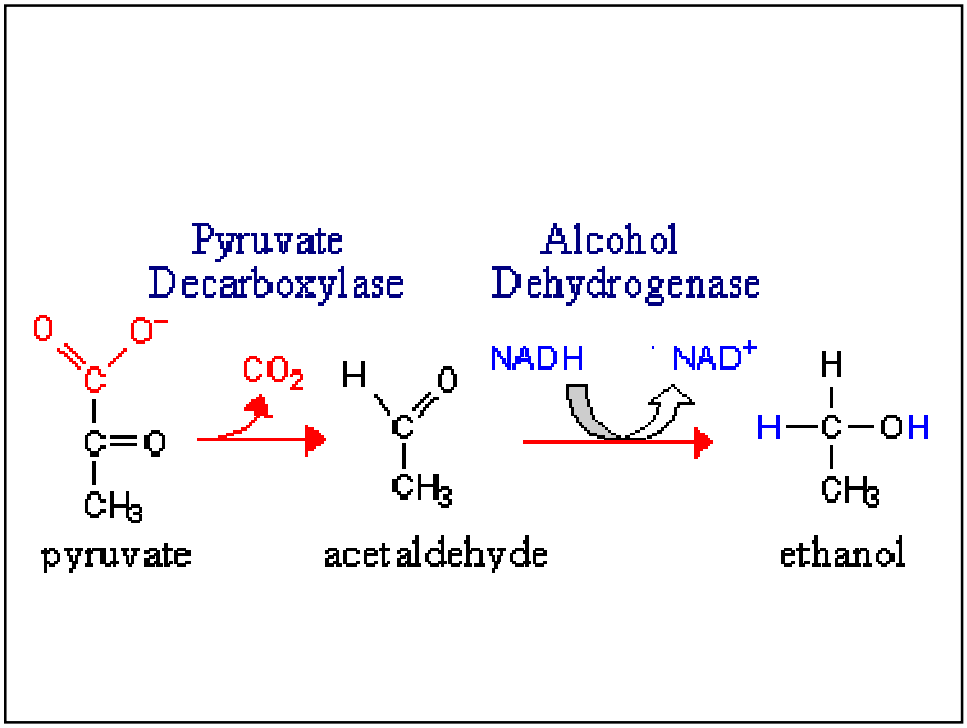
P_i attacks the thioester bond releasing the product

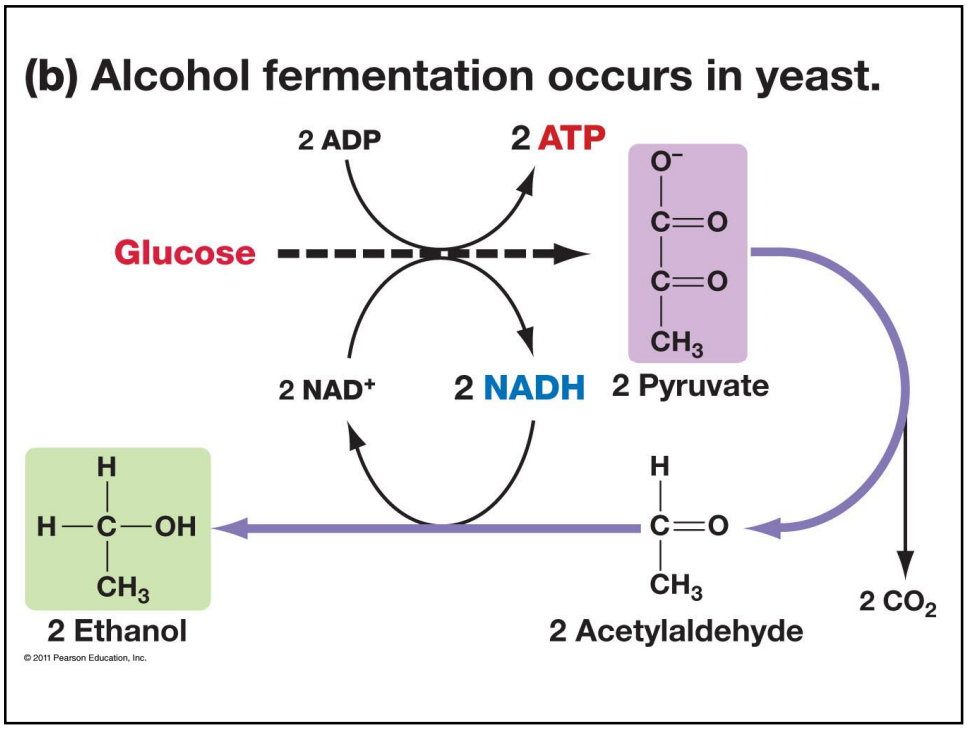

Phosphoglycerate kinase
+ ADP
+ ATP
1,3-Bisphosphoglycerate
3-Phosphoglycerate


Phosphoglycerate mutase
Enolase
Pyruvate kinase
ADP + H+
ATP
3-Phosphoglycerate
2-Phosphoglycerate
Phosphenolpyruvate
Pyruvate


Glucose 6-P
Glucose
Fructose 6-P
Fructose 1,6-bis-P
Glyceraldehyde 3-P
Dihydroxy acetone-P
1,3-bis-Phosphoglycerate
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenolpyruvate
Pyruvate
-ATP
-ATP
2 NADH
2 ATP
Is Oxygen needed?
2ATP


COO⁻
C=O
CH3
Pyruvate
NADH + H+
NADH + H+
Lactate dehydrogenase
NAD+
NAD+
COO⁻
H-C-OH
CH3
Lactate


Pyruvate
Decarboxylase
Alcohol
Dehydrogenase
CO_2
NADH
NAD^+
pyruvate
acetaldehyde
ethanol


(b) Alcohol fermentation occurs in yeast.
2 ADP
2 ATP
Glucose
$2\ NAD^+$
2 NADH
2 Pyruvate
2 Ethanol
2 Acetylaldehyde
$2\ CO_2$
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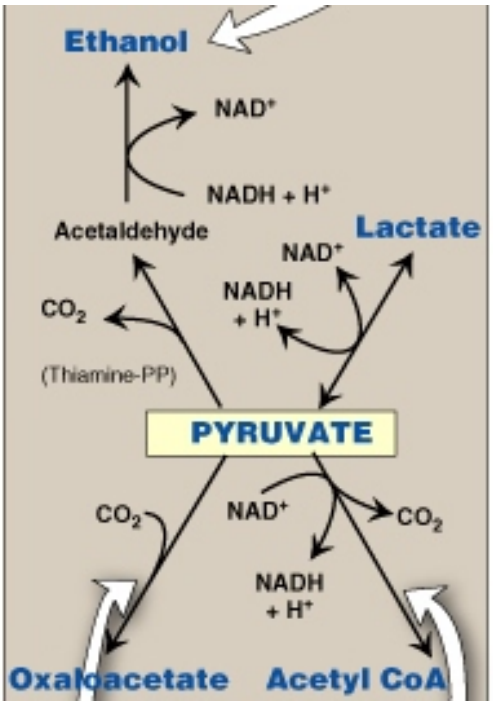


Lactate Production

- Cells with low energy demand
- To cope with increased energy demand in rigorously exercising muscle

  lactate level is increased 5 to 10 folds
- Hypoxia

  to survive brief episodes of hypoxia

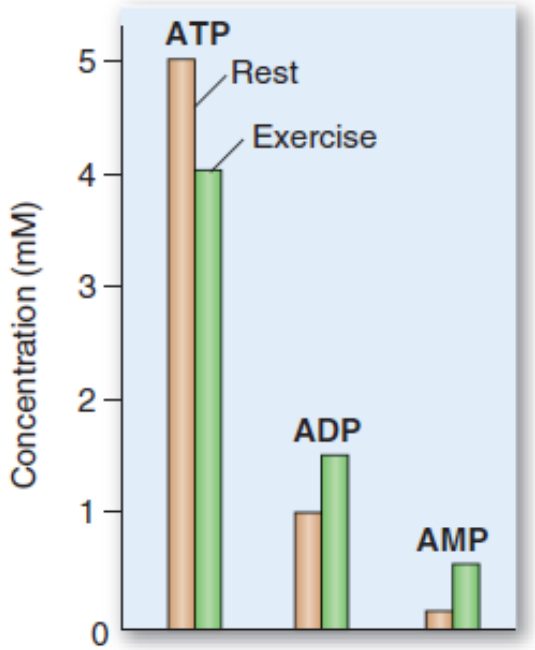
Lactic Acidosis

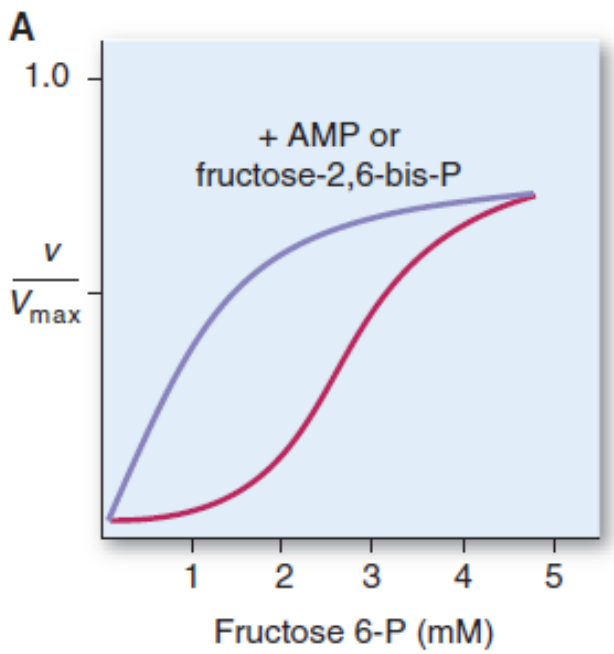
- ↓ pH of the plasma
- The most common cause of metabolic acidosis
  - ↑ Production of lactic acid
  - ↓ utilization of lactic acid

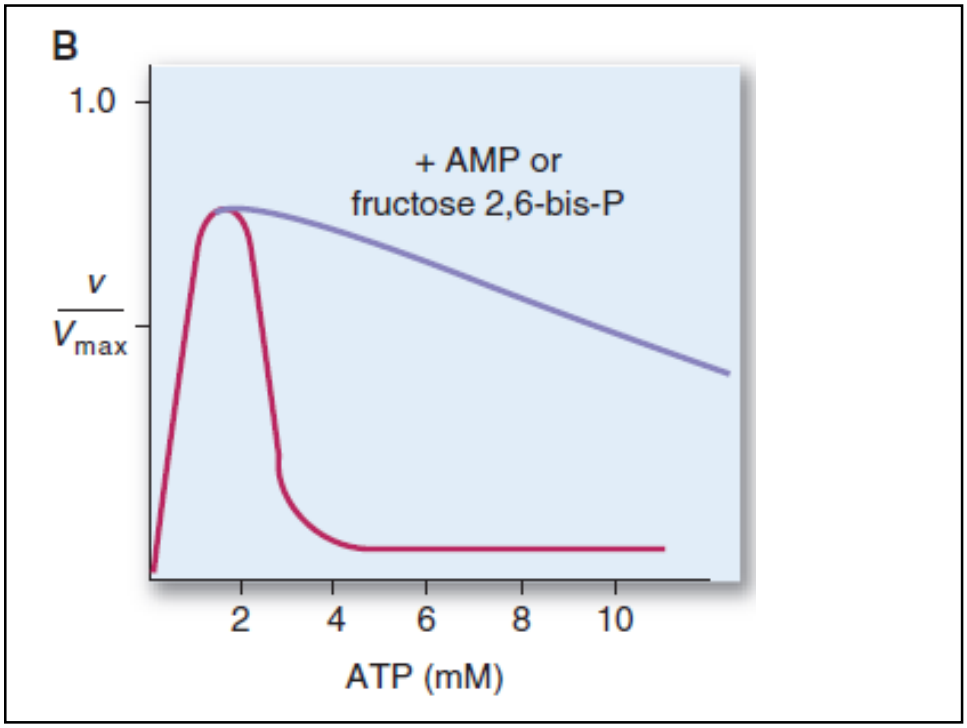
- Most common cause: Impairment of oxidative metabolism due to collapse of circulatory system.
  - Impaired O2 transport
  - Respiratory failure
  - Uncontrolled hemorrhage

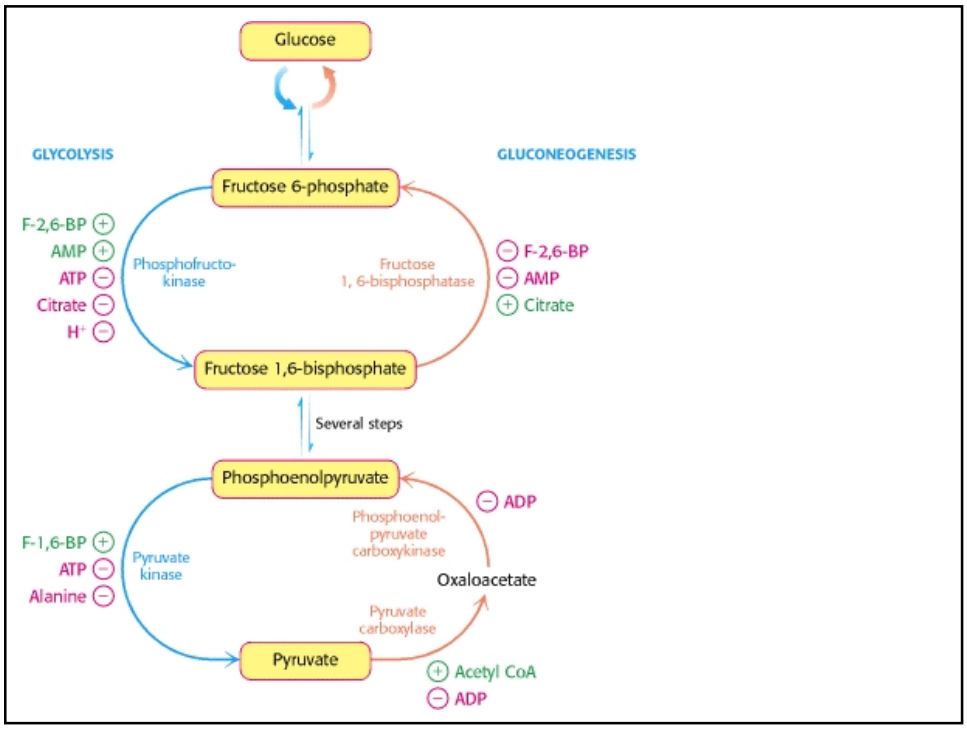
Lactic Acidosis

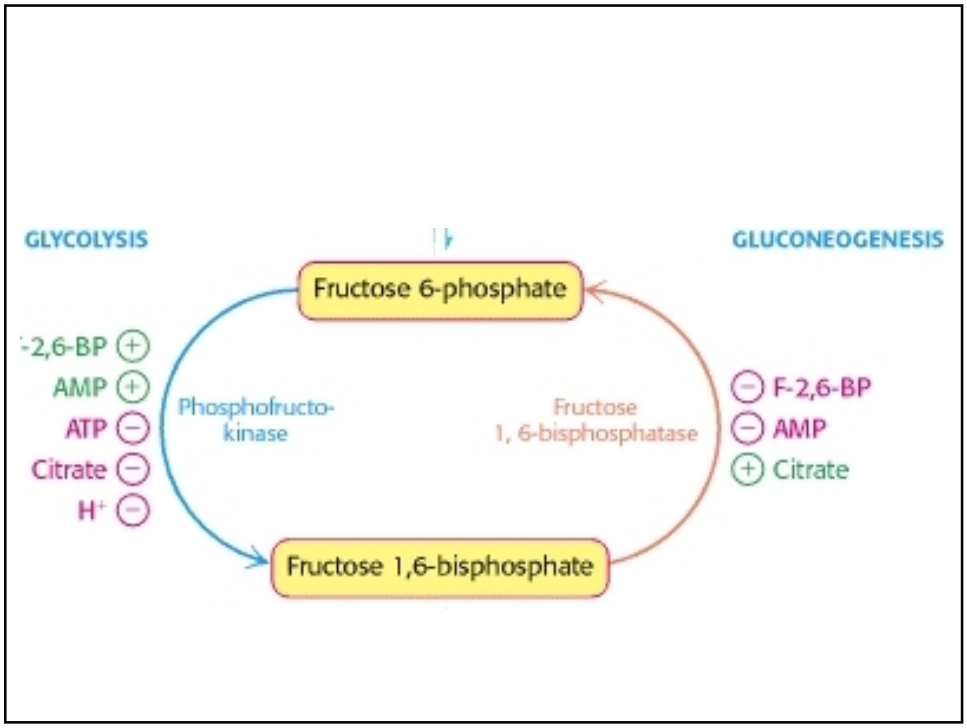
- Direct inhibition of oxidative phosphorylation
- Hypoxia in any tissuue
- Alcohol intoxication (high NADH/ NAD+)
- ↓ Gluconeogenesis
- ↓ Pyruvate Dehydorgenase
- ↓ TCA cycle activity
- ↓ Pyruvate carboxylase

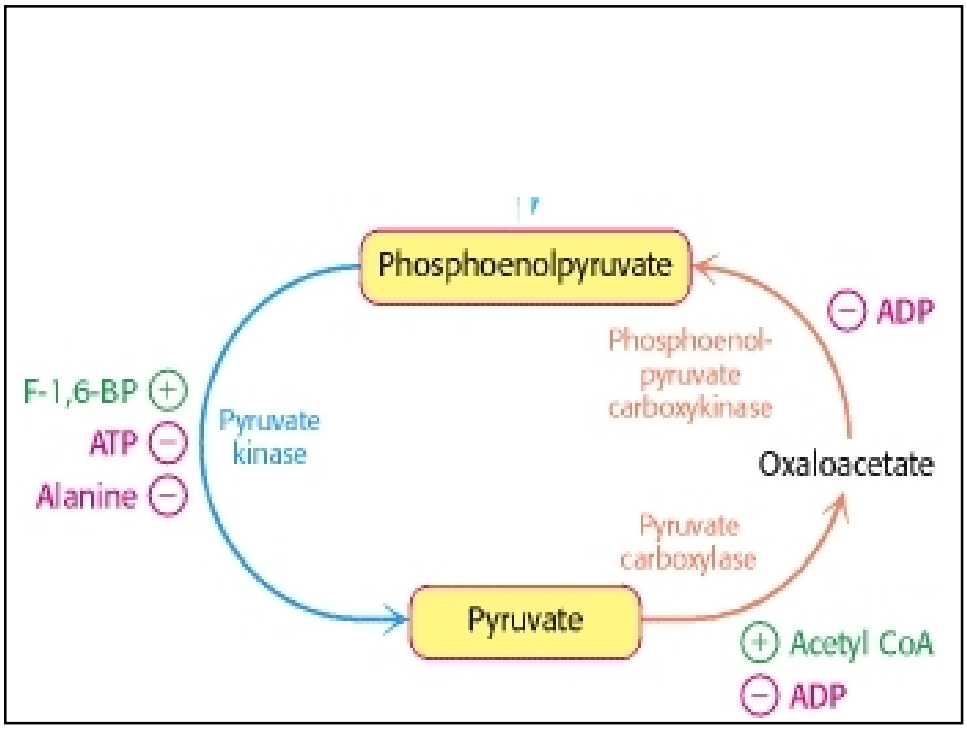

ATP
Rest
Exercise
ADP
AMP
Concentration (mM)
0
1
2
3
4
5

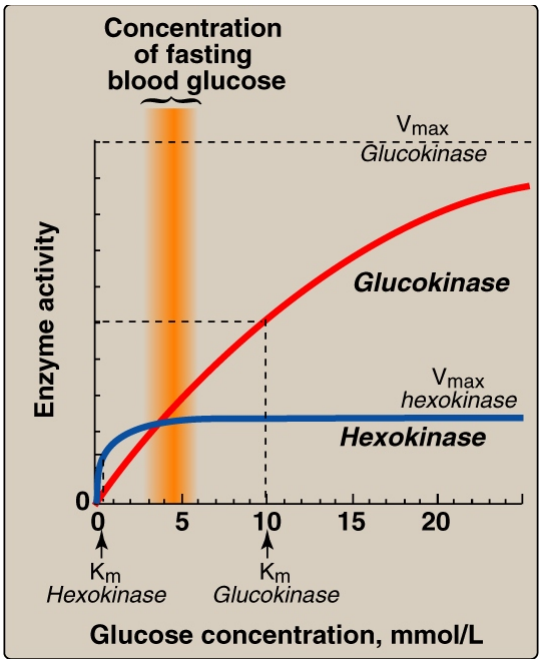

A
1.0
+ AMP or
fructose-2,6-bis-P
v
Vmax
1
2
3
4
5
Fructose 6-P (mM)

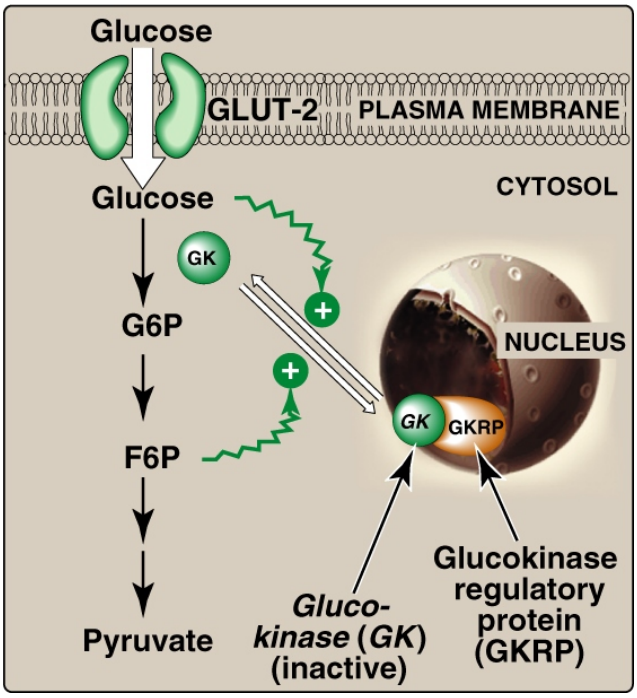

B
1.0
+ AMP or
fructose 2,6-bis-P
v
Vmax
2
4
6
8
10
ATP (mM)

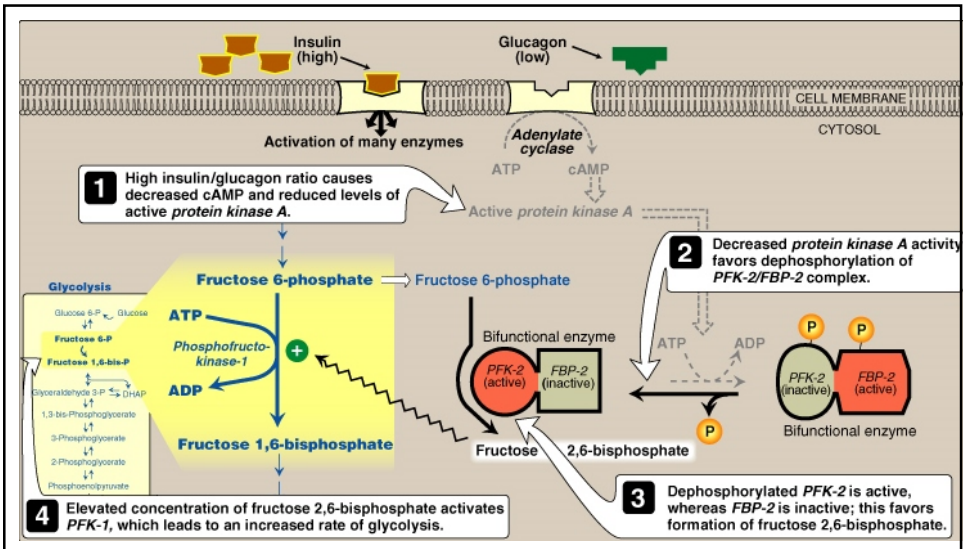

Glucose
GLYCOLYSIS
GLUCONEOGENESIS
Fructose 6-phosphate
F-2,6-BP
AMP
ATP
Citrate
H+
Phosphofructo-
kinase
Fructose
1, 6-bisphosphatase
F-2,6-BP
AMP
Citrate
Fructose 1,6-bisphosphate
Several steps
Phosphoenolpyruvate
ADP
Phosphoenol-
pyruvate
carboxykinase
F-1,6-BP
ATP
Alanine
Pyruvate
kinase
Oxaloacetate
Pyruvate
carboxylase
Pyruvate
Acetyl CoA
ADP


GLYCOLYSIS
GLUCONEOGENESIS
Fructose 6-phosphate
-2,6-BP +
AMP +
ATP −
Citrate −
H+ −
Phosphofructo-
kinase
Fructose
1, 6-bisphosphatase
− F-2,6-BP
− AMP
+ Citrate
Fructose 1,6-bisphosphate


Phosphoenolpyruvate
− ADP
Phosphoenol-
pyruvate
carboxykinase
F-1,6-BP +
ATP −
Alanine −
Pyruvate
kinase
Oxaloacetate
Pyruvate
carboxylase
Pyruvate
+ Acetyl CoA
− ADP


Concentration of fasting blood glucose
Vmax
Glucokinase
Glucokinase
Vmax
hexokinase
Hexokinase
Enzyme activity
0
0
5
10
15
20
Km
Hexokinase
Km
Glucokinase
Glucose concentration, mmol/L


Glucose
GLUT-2
PLASMA MEMBRANE
CYTOSOL
Glucose
GK
G6P
+
+
NUCLEUS
F6P
GK
GKRP
Pyruvate
Gluco-kinase (GK) (inactive)
Glucokinase regulatory protein (GKRP)


Insulin (high)
Glucagon (low)
CELL MEMBRANE
CYTOSOL
Activation of many enzymes
Adenylate cyclase
ATP
cAMP
1 High insulin/glucagon ratio causes decreased cAMP and reduced levels of active protein kinase A.
Active protein kinase A
2 Decreased protein kinase A activity favors dephosphorylation of PFK-2/FBP-2 complex.
Glycolysis
Fructose 6-phosphate
Fructose 6-phosphate
ATP
Phosphofructo-kinase-1
ADP
Fructose 1,6-bisphosphate
Bifunctional enzyme
PFK-2 (active)
FBP-2 (inactive)
ATP
ADP
P
PFK-2 (inactive)
FBP-2 (active)
Bifunctional enzyme
Fructose
2,6-bisphosphate
3 Dephosphorylated PFK-2 is active, whereas FBP-2 is inactive; this favors formation of fructose 2,6-bisphosphate.
4 Elevated concentration of fructose 2,6-bisphosphate activates PFK-1, which leads to an increased rate of glycolysis.